Docket No.: 085742-0486 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 20277
Bianca BROGMANN, et al.	:	Confirmation Number: 1883
Application No.: 10/510,673	:	Group Art Unit: 1615
Filed: May 23, 2005	:	Examiner: Caralynne HELM

For: MATRIX FOR SUSTAINED, INVARIANT AND INDEPENDENT RELEASE OF ACTIVE COMPOUNDS

DECLARATION UNDER 37 CFR 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Christian Leuner, hereby declare:

1. I am a German citizen and am more than twenty-one years of age.

2. I am Functional Director of Analytical and Pharmaceutical Sciences at Mundipharma Research GmbH & Co. A copy of my *curriculum vitae* is attached as Exhibit A.

3. Mundipharma GmbH & Co is a company associated with the instant assignee, Euro-Celtique S.A.

4. I am familiar with the specification and pending claims of U.S. Patent Application No. 10/510,673, filed May 23, 2005.

5. I have reviewed the Office Action mailed April 27, 2010 ("the Office Action"); European Patent Application No. 0699436 ("Miller"); U.S. Patent No. 4,457,933 ("Gordon"); U.S. Patent No. 6,306,438 ("Oshlack"); and U.S. Patent No. 5, 958,452 ("Oshlack B").

6. The Examiner states that Miller teaches an oral controlled release composition that releases the hydrochloride salt of the opioid analgesic tramadol, and an uncoated tablet including tramadol hydrochloride, ethyl cellulose, lactose, cetostearyl alcohol, magnesium stearate, and talc. Office Action, p. 5.

7. The Examiner states that Miller "specifically teaches the varying amounts of the matrix components (see page 4 lines 41-47), thus at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation." Office Action, p. 6.

8. The Examiner acknowledges that Miller does not teach the inclusion of an opioid antagonist in the composition. *Id.*

9. The Examiner states that Gordon teaches the combination of an opioid analgesic and antagonist in an oral composition. *Id.*

10. The Examiner states that both Miller and Gordon teach a sustained release oral opioid composition. Office Action, p. 7.

11. According to the Examiner, it would have been obvious to include naloxone in the composition of Miller because Gordon teaches that compounds such as oxycodone and tramadol are subject to abuse. *Id.*

12. The Examiner states that Oshlack teaches a composition similar to that of Miller, wherein ethyl cellulose is combined with stearyl alcohol, tramadol hydrochloride, and other excipients. *Id.*

13. The Examiner states that invariant and independent release "are viewed as properties of the composition based upon its constituent materials." Office Action, p. 8.

14. One of ordinary skill in the art at the time the instant invention was filed would have understood that Gordon does not teach a sustained release oral opioid composition in its general or specific disclosure. For example, the excipients recited in column 1, lines 5-21 of Gordon do not provide sustained release.

15. I understand that to help define or understand a claim term, one may look to the specification for guidance.

16. The instant specification states that "'independent release' means that, given the presence of two active compounds, a change in the absolute amount of one compound does not influence the release profiles of the other compounds so that the release profiles of the other compounds are not changed." Specification, para. 42.

17. The instant specification states that "invariant release profile" means that "the percentage of the absolute amount of each active compound released per time unit does not significantly change and remains sufficiently constant (and does not substantially change) if absolute amounts are changed." Specification, para. 46.

18. "Independent" and "invariant" preparations can "differ with respect to the amount of the active compounds, but are of the same or at least highly similar composition with respect to the release-influencing components of the preparation. Typically, the difference in the amount of an active compound will be replaced by the amount of a pharmaceutical inert excipient which does not substantially influence the release behaviour of the preparation." Specification, para. 48.

19. The specification states that lactose is one example of a pharmaceutically inert excipient. Specification, para. 48.

20. One of ordinary skill in the art would have understood that the release profile of an agent, whether active or inert, from a matrix depends on the physical chemistry properties of the agent in relation to the release-influencing components and other agents within the formulation, and not the functional properties of the agents alone. Such physical chemistry properties are drug specific and include, for example, the diffusion coefficient, pK, solubility, molecular weight, hydrogen donor and acceptor sites, and the partition coefficient.

21. In accordance with paragraph 20 above, the prior art references suggesting (according to the Examiner) that one of ordinary skill in the art would combine an opioid agonist and an opioid antagonist into the claimed formulations is inapplicable here. The functional properties (i.e., opioid agonism and antagonism) of the active agents as such are not pertinent to whether a formulation such as instantly claimed would reasonably be expected to provide "independent" and "invariant" release.

22. In addition to release of two active agents from the matrix according to the instant invention, inert pharmaceutical excipients such as lactose would also be released. One of ordinary skill in the art would have understood that the release of the pharmaceutically inert excipient is also dependent on its physical chemistry properties in relation to the release-influencing components, the active agents, and any other agents within the formulation.

23. Miller discloses a composition containing one active agent. One of ordinary skill in the art at the time the instant application was filed would not have reasonably predicted, nor had a reasonable expectation, that a composition according to Miller, modified in accordance with Gordon, would provide formulations comprising two active agents having "independent" and "invariate" release.

23a. For the reasons provided in paragraphs 14-23, above, the addition of Oshlack to the combined teachings of Miller and Gordon does not disclose, suggest, or render predictable the claimed plurality of formulations, which release the active compounds in an independent and invariate manner, because Oshlack discloses a composition similar to that of Miller. See Office Action, p. 7.

24. The Examiner states that Oshlack B teaches oral sustained release opioid formulations, which include ethyl cellulose, tibutyl citrate, stearyl alcohol, talc, and magnesium stearate. The Examiner acknowledges that Oshlack B does not disclose the presence of an opioid antagonist in its formulations along with an opioid agonist. Office Action, p. 9-10.

25. The Examiner states that it would have been obvious to include an opioid antagonist in the oxycodone composition of Oshlack B because Gordon teaches that oxycodone compositions are prone to abuse. Office Action, p. 10.

26. For the same reasons stated in paragraphs 16 - 22, above, one of ordinary skill in the art at the time the instant application was filed would not have reasonably predicted, nor had a reasonable expectation, that a composition according to Oshlack B (containing one active agent), modified in accordance with Gordon, would provide formulations comprising two active agents having "independent" and "invariate" release.

27. Based on a reference (e.g., Miller or Oshlack B) disclosing one active agent and a release-influencing component, one of ordinary skill in the art could not have predicted, nor reasonably expected, that the release properties of *two* active agents would remain constant, i.e., invariant, when the amounts of the active agents are changed but the amount of release-influencing component is kept the same or highly similar.

28. In accordance with paragraphs 7 to 27 above, Miller and Oshlack B, in combination with Gordon, do not disclose or suggest a plurality of formulations wherein two active agents and an inert pharmaceutical excipient may be altered in amount but maintain the same release profile.

29. I declare further that statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 26. OKT. 2010

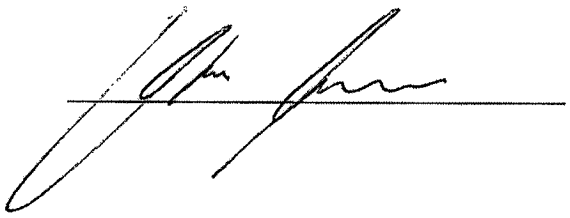

Exhibit A

Dr. Christian Leuner is the Functional Director of Analytical and Pharmaceutical Sciences of Mundipharma Research GmbH & Co. KG since April 2004. He joined Mundipharma in July 2003 as Head of Pharmaceutical Formulation & Clinical Supplies. In his position he is responsible for leading the analytical and pharmaceutical development in national and international research projects. The development focuses on the development of oral solid and liquid dosage forms and topical semisolid formulations. The department is structured in a formulation, a clinical supply and two analytical groups with a total number of 24 employees. Before he joined Mundipharma he completed a doctoral thesis "Solid dispersions improve the biopharmaceutical properties of itraconazole" in the research group of Prof. Dr. J. B. Dressman at the Institute for Pharmaceutical Technology, J.W. Goethe University in Frankfurt. Prior to beginning his doctoral studies, he worked on a placement in the Pharmaceutical R&D department at Merz+Co., Frankfurt.

He has presented his work at AAPS and APV, he has published a review article on solid solution dosage forms and was coauthor of four research articles. Dr. Leuner was invited speaker at FIP International Workshop Dissolution of Special Dosage Forms and Conference on; Drug Delivery & Diffusion through Polymers by Institute of Physics, Imperial College, London; 3rd International Symposium on Pharmaceutical Melt Extrusion, APV short course on development, Stability Testing and Manufacture of Narcotics. At Frankfurt University he was responsible teaching in the area of parenterals, eye drops and lyophilisation. In 2000, 2002 and 2003 he was lecturer and instructor at the postgraduate diploma course: radiopharmaceutical chemistry/ radiopharmacy. He is head lecturer of the module Drug Discovery and Development at University Duisburg-Essen as part of a MSc in Pharmaceutical Medicine. He is also regularly lecturing as part of the GMP course at Frankfurt University and Dr. Leuner has the qualification as a qualified person according the German drug law §14 and is member of the APV and AAPS.